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EXAMINER	
SHEN, WU CHENG WINSTON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,299	KOLLET ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *1-29,37 and 40-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-36,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's claim amendments filed on 10/12/2009 have been entered.

Claims 1-62 are pending. Claims 30, 38, 39, 41, 43, 61, and 62 are amended.

Claims 1-29, 37, and 40-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/06/2009.

Claims 30-36, 38, and 39 are currently under examination to the extent of stem cells being hematopoietic stem cells.

This application 10/552,299 filed on 08/25/2006 is a 371 of PCT/IL04/00314 filed on 04/07/2004, which claims the benefits of foreign applications ISRAEL 155302 filed on 04/08/2003 and ISRAEL 159306 filed on 12/10/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Previous rejection of claims 30-36, 38 and 39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Amended claim 30 filed on 10/12/2009 no longer recites the limitation "isolating stem cells having CXCR4 levels above a predetermined threshold". Claims 31-36, 38 and 39 depend from claim 30.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Previous rejection of claims 30-36, 38, and 39 under 35 U.S.C. 102(b) as being anticipated by **Kollet et al.** (Kollet et al., Rapid and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, *Blood* 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007) as evidenced by **Janowska-Wieczorek et al.** (Janowska-Wieczorek et al., Growth factors and cytokines upregulate gelatinase expression in bone marrow CD34(+) cells and their transmigration through reconstituted basement membrane, *Blood*, 93(10):3379-90, 1999; this reference is listed as reference C31 in the IDS filed by Applicant on 01/29/2007), is ***withdrawn*** because the claims have been amended.

Amended claim 30 filed on 10/12/2009 reads as follows: A method of generating stem cells suitable for transplantation, the method comprising: (a) collecting stem cells;
(b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof;

and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation.

Neither Kollet et al. (2001) nor Janowska-Wieczorek et al. (1999) teaches the amended limitation "exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof".

3. Previous rejection of claims 30-36, 38, and 39 under 35 U.S.C. 102(b) as being anticipated by **Kollet et al.** (Kollet et al., The plant lectin FRIL supports prolonged in vitro maintenance of quiescent human cord blood CD34(+)CD38(-/low)/SCID repopulating stem cells, *Exp Hematol.* 28(6):726-36, 2000) as evidenced by **Janowska-Wieczorek et al.** (Janowska-Wieczorek et al., Growth factors and cytokines upregulate gelatinase expression in bone marrow CD34(+) cells and their transmigration through reconstituted basement membrane, *Blood*, 93(10):3379-90, 1999; this reference is listed as reference C31 in the IDS filed by Applicant on 01/29/2007), is ***withdrawn*** because the claims have been amended.

Amended claim 30 filed on 10/12/2009 reads as follows: A method of generating stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation.

Neither Kollet et al. (2000) nor Janowska-Wieczorek et al. (1999) teaches the amended limitation "exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 30-36, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kollet et al.** (Kollet et al., Rapid and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, *Blood* 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007) in view of **Heissing et al.** (Heissing et al. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand, *Cell* 109(5):625-37, 2002), **Togawa et al.** (Togawa et al., Highly activated matrix metalloproteinase-2 secreted from clones of metastatic lung nodules of nude mice injected with human fibrosarcoma HT1080, *Cancer Lett.* 146(1):25-33, 1999), **Rafii et al.** (US 2004/0071687, publication date 04/15/2004, filed on 05/28/2003, provisional application 60/383,658 file don 05/28/2002), and **Sadatmansoori et al.** (Sadatmansoori et al. Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix Metalloproteinase-9, *Protein Expr Purif.* 23(3):447-52, 2001). *This rejection is necessitated by claim amendments filed on 10/12/2009.*

Amended claim 30 filed on 10/12/2009 reads as follows: A method of generating stem cells suitable for transplantation, the method comprising: (a) collecting stem cells;

(b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation.

Claim interpretation: The limitation "exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof" recited in claim 30 reads on exposure to (i) any amount of a matrix metalloprotease expressed by exogenous nucleic acid molecule of collected stem cells, or (ii) any amount of matrix metalloprotease polypeptide added exogenously to the collected stem cells, and the matrix metalloprotease polypeptide does not need to be purified. For instance, the matrix metalloprotease polypeptide may be from the media cultured with cells that secret matrix metalloprotease polypeptide. The (ii) possibility is consistent with Example 4 disclosed in instant application, which indicates addition of supernatant of HT1080 cell line, which secrete MMP-2 and MMP-9, to pre BLL cell G2.

Kollet et al. teaches that during development hematopoietic stem cells migrate from the fetal liver into the bone marrow (BM) and continuously produce maturing hematopoietic cells that are released into the blood circulation. Hematopoietic stem cells are functionally defined, based on their ability to home to the BM microenvironment and to durably repopulate transplanted recipients with both myeloid and lymphoid cells (See Introduction, page 3283, Kollet et al., 2001).

With regard to step (a) of claim 30 and limitations of claims 34-36, Kollet et al. teaches isolation of CD34+ hematopoietic stem cells from human cord blood (CB) sample using the MACS cell isolation kit and MidiMacs columns. Isolated $CD34^+$ cells were either used immediately for homing experiments or after overnight incubation with RPMI supplemented

with 10% fetal calf serum (FCS) and stem cell factor (SCF) (50 ng/mL). In both cases only primitive $CD34^{+}CD38^{-/low}$ cells homed in vivo. (See Materials and methods, left column, page 3284, Kollet et al., 2001).

With regard to step (c) of claim 30 and limitation of claim 39 pertaining to treatment leading to increased CXCR4 levels in hematopoietic stem cells, Kollet et al. teaches that enriched $CD34^{+}$ cells were further labeled with human specific monoclonal antibody (mAb) anti-CD34 FITC (Becton Dickinson, San Jose, CA) and anti-CD38 PE (Coulter, Miami, FL) and sorted for $CD34^{+}CD38^{-/low}$- or $CD34^{+}CD38^{+}$-purified subpopulations by FACStar^{+} (See Materials and methods, left column, page 3284, Kollet et al., 2001), and homing of enriched human $CD34^{+}$ cells was inhibited by pretreatment with anti-CXCR4 antibodies, moreover, primitive $CD34^{+}CD38^{-/low}CXCR4^{+}$ cells also homed in response to a gradient of human stromal cell-derived factor 1 (SDF-1), directly injected into the bone marrow or spleen of non-irradiated NOD/SCID mice (See abstract, page 3283, Kollet et al., 2001). Kollet et al. teaches that *ex vivo* cytokine-stimulated CB (cord blood) $CD34^{\pm}CD38^{\pm}$ cells had increased CXCR4 expression as well as improved migration capacities toward a gradient of SDF-1 and also could transiently home to the BM of NOD/SCID mice but failed to durably repopulate it for 1 month. The chemokine SDF-1 was shown to attract immature human $CD34^{+}$ cells *in vitro*. Primitive $CD34^{+}CD38^{-/low}$ cells express higher levels of CXCR4 compared to $CD34^{+}CD38^{+/high}$ cells. Kollet et al. demonstrated a positive correlation between CXCR4 expression and SDF-1-induced transendothelial migration of leukemic cells. In correlation with these results, Kollet et al. showed that freshly isolated CB $CD34^{+}CD38^{-/low}$ cells migrate better to SDF-1 compared to more mature $CD34^{+}CD38^{+}$ cells, which also secrete low levels of SDF-1. Kollet et al. further

demonstrated that human SRC/stem cell engraftment of NOD/SCID mice is dependent on CXCR4/SDF-1 interactions. Kollet et al. teaches that, therefore, the involvement of SDF-1/CXCR4 interactions in SRC/stem cell homing is of interest. Blocking of CXCR4 signaling on transplanted $CD34^+$-enriched cells prevented homing, whereas pretreatment of cells with cytokines (e.g. SDF-1) lead to up-regulation of CXCR4 expression, which increased both in vitro migration to SDF-1 and in vivo homing. CXCR4-dependent homing was observed in the BM and spleen of engrafted mice but not in the lungs (See bridging paragraph pages 3288-3289, Kollet et al., 2001).

With regard to collecting stem cell effected by mobilization procedure recited in claim 31, Kollet et al. teaches an homing assay in which human $CD34^+$-enriched cells were either labeled prior to transplantation with the fluorescent dye PKH26-GL (2 μL PKH26-GL were added to 1-10 $\times$ 10^6 $CD34^+$ cells in a total volume of 1 mL Diluent C) or transplanted without pre-labeling. Transplantation cell dose of $CD34^+$-enriched cells was: 0.5-1 $\times$ 10^6 cells/mouse; sorted $CD34^+CD38^{-/low}$ cells: 2 $\times$ 10^5 cells/mouse (Figure 1B, R2). Cells were recovered from the BM, spleen, or lungs of transplanted mice at time points as indicated and were analyzed for the presence of either $PKH26^+$ or human cells by flow cytometry acquiring 10^6 cells per sample (FACScalibur) (See right column, page 3284, Kollet et al., 2001).

Kollet et al. does not explicitly teaches **(I)** the limitation "exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof" recited in step (b) of claim 30, which correlates with increased CXCR4 levels recited in step (c) of claim 30, and **(II)** the limitation "wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix

metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof, as recited in claim 38.

(I) With regard to connection between cytokine (SDF-1 taught by Kollet et al., 2001) and matrix metalloprotease (MMP-9 taught by Heissig et al., 2002), and its functional role in differentiation and mobilization of hematopoietic stem cells (HSCs), **Heissig et al.** teaches that stem cells within the bone marrow (BM) exist in a quiescent state or are instructed to differentiate and mobilize to circulation following specific signals. Matrix metalloproteinase-9 (MMP-9), induced in BM cells, releases soluble Kit-ligand (sKitL), permitting the transfer of endothelial and hematopoietic stem cells (HSCs) from the quiescent to proliferative niche. BM ablation induces SDF-1, which upregulates MMP-9 expression, and causes shedding of sKitL and recruitment of c-Kit+ stem/progenitors (See abstract and Figure 8, shown below, Heissig et al. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand, *Cell* 109(5):625-37, 2002).

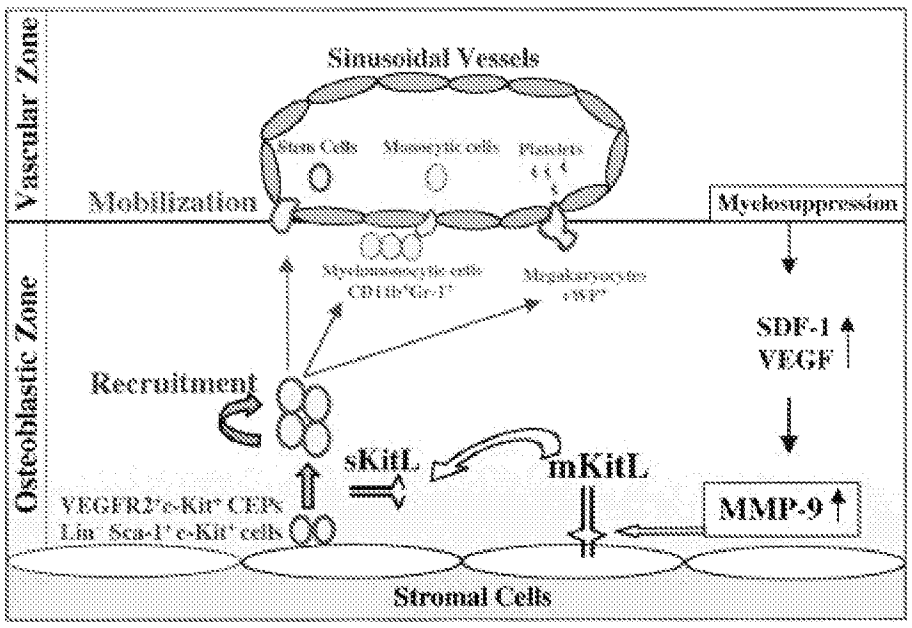

Figure 8. Functional Anatomy and Recruitment of c-Kit$^+$ Stem and Progenitor Cells Is Dictated by MMP-9 Mediated Release of sKitL Under steady-state conditions quiescent c-Kit$^+$ HSCs and CEPs reside in a niche in close contact with stromal cells including osteoblasts. Membrane-bound cytokines, such as mKitL not only convey survival signals, but also support the adhesion of stem cells to the stroma. BM ablation or chemokine/cytokine administration induces upregulation of MMP-9 resulting in the release of sKitL. sKitL confers signals that enhances mobility of VEGFR2$^+$ endothelial progenitors (CEPs) and Lin$^-$Sca-1$^+$c-Kit$^+$ repopulating cells, translocating them into a vascular-enriched niche favoring differentiation and mobilization to the peripheral circulation.

The teachings of Heissig et al. provides the molecular mechanism underlying the teachings by Kollet et al., 2001 regarding effects of pretreatment of cells with cytokines SDF-1 lead to up-regulation of CXCR4 (SDF-1 receptor) expression, which increased both *in vitro* migration to SDF-1 and *in vivo* homing of hematopoietic stem cells (HSCs). Based on combined teachings of Kollet et al. and Heissig et al., HSCs differentiation and mobilization requires increased SDF-1 and CXCR4 levels and their interaction as well as increased MMP-9. Therefore, addition of an exogenous matrix metalloprotease, which includes MMP-9 that function downstream of increased SDF-1/CXCR4 interaction, is expected to facilitate generation of hematopoietic stem cells (HSCs) suitable for transplantation as recited in claim 30 of instant application. This functional link between SDF-1/CRCR4 interaction and MMP-9 is further supported by the teachings of Rafii et al. (US 2004/0071687) that MMP-9 promotes release of stem cell active cytokines, as discussed in more details in **(II)** below.

With regard to the source of exogenous matrix metalloproteases recited in step (b) of claim 30, and the limitation "wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by contacting said stem cells with said

matrix metalloprotease or said active portion thereof, as recited in claim 38, **Togawa et al.** teaches that the supernatant of monolayer culture of human fibrosarcoma cells (HT1080) contain functionally active MMP-2 and MMP-9 (See abstract, Togawa et al., Highly activated matrix metalloproteinase-2 secreted from clones of metastatic lung nodules of nude mice injected with human fibrosarcoma HT1080, *Cancer Lett.* 146(1):25-33, 1999).

(II) With regard to the limitation "wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells, as recited in claim 38, **Rafii et al.** (US 2004/0071687) teaches that *MMP-9 promotes release of stem cell active cytokines (e.g. SDF-1), thereby promoting expansion of quiescent stem cells, and this novel concept lays the foundation of developing strategies where activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization* (See paragraph [0114], US 2004/0071687). It is worth noting that the combined teachings of Heissig et al. and Rafii et al. discloses a functional positive feedback loop of increased SDF-1/CXCR4 interaction and increased MMP-9 expression in regulation of hematopoietic stem cells (HSCs) mobilization and differentiation. Rafii et al. (US 2004/0071687) further teaches DNA constructs, adenoviral vector, expressing various cytokines, including AdSDF-1 and AdVEGF (See for instance, paragraph [0165], US 2004/0071687). Furthermore, **Sadatmansoori et al.** teaches DNA construction, baculovirus expression, and partial characterization of a minienzyme form of the human matrix metalloproteinase-9 (MMP-9). (See abstract, Sadatmansoori et al.

Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix Metalloproteinase-9, *Protein Expr Purif.* 23(3):447-52, 2001).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Kollet et al. regarding isolation and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, with (i) the teachings of Heissig et al. regarding Matrix metalloproteinase-9 (MMP-9), induced in BM cells, releases soluble Kit-ligand (sKitL), permitting the transfer of endothelial and hematopoietic stem cells (HSCs) from the quiescent to proliferative niche. BM ablation induces SDF-1, which upregulates MMP-9 expression, and causes shedding of sKitL and recruitment of c-Kit+ stem/progenitors, (ii) the teachings of Togawa et al. regarding highly activated MMP-9 and MMP-2 secreted from clones of metastatic lung nodules of nude mice injected with human fibrosarcoma HT1080, (iii) the teachings of Rafii et al. regarding MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization, and (iv) the teachings of Sadatmansoori et al. regarding construction and expression of human matrix metalloproteinase-9 (MMP-9), to arrive at the methods recited in claims 30-36, 38, and 39 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Kollet et al., Heissig et al., Togawa et al., Rafii et al., and Sadatmansoori et al. because (i) Rafii et al. teaches MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and activation of MMP-9 may act as molecular switches to

expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization, (ii) Heissig et al. teaches the molecular mechanism underlying the observations by Kollet et al., 2001 in term of a functional role of MMP-9 in the effects of pretreatment of cells with cytokines SDF-1 leading to up-regulation of CXCR4 expression, which increased both *in vitro* migration to SDF-1 and *in vivo* homing of hematopoietic stem cells (HSCs), and (iii) Togawa et al. and Sadatmansoori et al. teaches the feasibility of obtaining an exogenous matrix metalloprotease, MMP-9, either from supernatant of HT1080 cell culture or from molecular cloning the expression of polynucleotide expressing MMP-9.

There would have been a reasonable expectation of success given (i) successful demonstration of isolation and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, by the teachings of Kollet et al., (ii) successful demonstration of increased SDF-1/CXCR4 and MMP-9 and their molecular interactions during the process of HSC differentiation and mobilization, by the combined teachings of Heissig et al. and Rafii et al., and (iii) successful demonstration of obtaining an exogenous matrix metalloprotease, MMP-9, either from supernatant of HT1080 cell culture or from molecular cloning the expression of polynucleotide expressing MMP-9, the combined teachings of Togawa et al. and Sadatmansoori et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of

obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Kollet et al., Heissig et al., Togawa et al., Rafii et al., and Sadatmansoori et al. have been clearly set forth above in this office action.

Conclusion

5. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632